(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 508 969 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **92850062.8**

(51) Int. Cl.[5] : **A61K 9/72**

(22) Date of filing : **24.03.92**

(30) Priority : **11.04.91 SE 9101090**

(43) Date of publication of application :
14.10.92 Bulletin 92/42

(84) Designated Contracting States :
PT

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(54) Process for conditioning of water-soluble substances.

(57) A Process for providing water-soluble micronized substances, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such stubstances, which process is carried out by

a) reducing, if necessary, the residual water from the micronized substance by drying optionally at an elevated temperature and/or vacuum,

b) conditioning said dried, micronized substances with a solvent, and

c) eliminating residual solvent by storing in a dry place like vacuum or by purging with an inert gas.

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Field of the invention

The present invention relates to a process for providing water-soluble micronized substances, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such substances and which have improved physicochemical properties in the dry state, thereby facilitating the technical handling and significantly increasing the medical value of the substances.

Background of the invention

During the past few years, there have been frequent demonstrations of the fact that the appropriate selection of the most suitable crystalline modification significantly can influence the clinical results of a given chemical entity. The chemical and physical stability of a solid compound in a particular dosage form can be modified by presenting the substance in the appropriate crystal form. Little information is available on the role of polymorphism and crystal habit in solid dosage form and powder technology. It is, however, apparent that the appropriate selection of the most suitable crystalline modification, whether arising from polymorphic differences or as a result of solvate complex formation of both water-soluble substances and less water-soluble substances, such as theophylline, often significantly can increase the medical value of a given drug in a particular dosage form. There are only a few statements available to predict the outcome of a crystallization procedure if e.g. the substance could be involved in different polymorphic or pseudopolymorphic forms. Solid-state transformations may also occur during mechanical treatment, e.g. micronization and by pressure during tableting. While a few generalizations can be made concerning the influence of structural modifications on the tendency of a chosen compound to exhibit polymorphism or other phenomena, a complete understanding of this problem awaits further research. Often "trial and error" approaches are used to develop a successful formulation of a drug. It is necessary to establish the conditions whereby different forms of a substance might be converted to a single form thus eliminating differences in solid-state properties and subsequent different physico-chemical properties.

E. Shefter and T. Higuchi have measured the relative rates of dissolution of several crystalline solvated and non-solvated forms of important pharmaceuticals, J. Pharm. Sci., **52** (8), (1963), 781-91.

L. van Campen, G. Zografi and J.T. Carstensen give in a review article an approach to the evaluation of hygroscopicity for pharmaceutical solids, Int. J. Pharmceut. **5**, (1980), 1-18.

C. Ahlneck and G. Zografi describe the molecular basis of moisture on the physical and chemical stability of drugs in the solid state, Int. J. Pharmceut., **62**, (1990), 87-95.

M. Otsuka et al. have calculated hydration data using various solid-state kinetic models for theophylline anhydrate powder, J. Pharm. Pharmacol., **42**, (1990), 606-610.

Hak-Kim Chan and Igor Gonda have examined the properties of respirable crystals of cromoglycic acid by using different methods, J. Pharm. Sci., **78** (2), (1989), 176-80.

A more comprehensive discussion of factors relating to pharmaceutical preformulations and the physicochemical properties of drug substances is given by J.I. Wells in Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances, John Wiley & Sons, New York (1988). See particularly the chapter about polymorphism pp 86-91.

Brief description of the invention

The object of the invention is to provide a process for water-soluble micronized substances, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such substances, whereby reducing the residual water from the micronized substances, conditioning said dried, micronized substances with a solvent and finally eliminating residual solvent from the substances.

Detailed description of the invention

The object of the present invention is to provide a reliable process, where the desired polymorphic form can be conveniently and reproducibly prepared. The invention relates to a three step procedure:

a. reducing, if necessary, the residual water from the micronized substance by drying optionally at an elevated temperature and/or vacuum.

b. conditioning said dried micronized substance with a solvent, and

c. eliminating the residual solvent by storing the substance in a dry place, such as vacuum, or by purging with an inert gas.

The solvents used in the conditioning step b) are organic alcohols, ketones, esters, acetonitrile and the

like, most preferably lower alcohols like methanol, ethanol, n-propanol, isopropanol; lower ketones like acetone, methylethylketone; ethylacetate, preferably in the vapour phase.

According to one preferred embodiment the conditioning step b) is carried out in an inert gas containing solvent vapour.

The inert gas used in step c) and optionally in step b) is preferably nitrogen.

The preferred substances on which the invention is to be applied are carbohydrates, amino acids and drugs.

Carbohydrates, such as lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, xylitol, mannitol, myoinositol and the like, and amino acids, such as alanine, betaine and the like, are often used as additives in pharmaceutical compositions e.g. as additives in certain inhalation formulations.

Terbutaline sulfate, salbutamol sulfate, fenoterol hydrobromide and bambuterol hydrochloride are highly selective β_2-adrenergic agonist having bronchospasmolytic effect and are effective in the treatment of reversible obstructive lung ailments of various genesis, particularly asthmatic conditions. Disodium chromoglycate (DSCG) has been used as a prophylactic agent in the treatment of allergic bronchial asthma for many years.

The invention will be described by using lactose, terbutaline sulfate and salbutamol sulfate as examples.

The phenomena of solvate formation and polymorphism are well recognized in the literature in the preformulation studies in the development phase for new drugs in the solid state. e.g. the US Pharmacopoeia recognizes >90 drug hydrates!

Many substances exist in different polymorphs (pseudopolymorphs) and several metastabile solvates with variable composition and physical properties like bulk density and hygroscopicity. Several transformations between these polymorphs may occur at different velocity. These effects are operating when crystalline substances have been activated by various processes such as grinding, freeze drying, micronization or recrystallization to produce regions of partial amorphous structure. The substances often will be obtained in an amorphous state or a metastable crystalline form when spray drying, freeze drying, rapid solvent quenching or when using controlled precipitation where both crystalline and amorphous forms can be prepared. The use of an amorphous form or a metastable crystalline form is often limited due to its thermodynamic instability. It is therefore a desire to convert the amorphous form or the metastable crystalline formto the more stable crystalline state. The present invention deals with such physical and chemical changes, or more importantly, to anticipate them and the means by which these solid-state phenomena can be handled.

After recrystallization (or after spray drying/freeze-drying) the substance has to be micronized to the final particle size required for e.g. inhalation. The particles should be less than 100 µm and preferably less than 10 µm. For crystalline substances, the micronization step seems to give an amorphous outer layer of the particle making the particle more sensitive to moisture.

It is an object of this invention to be able to reliably provide a crystalline form of certain water-soluble substances, which can be produced, stored and used, while maintaining the aerodynamic properties and specifications (particle size, particle form, hygroscopicity etc) required for inhalation of such substances. The particle size of the micronized substances is identical before and after the conditioning step as measured by different instruments like Malvern Master Sizer, cuiter counter or a microscope.

The conditioning of the substance probably rearrange the outer layer of the crystals or the amorphous substance giving a more stable and less hygroscopic product.

In some instances it has been possible to use infrared spectroscopy in order to study the conversion of an amorphous form or a partly crystalline form into a stable crystalline form. Other methods available include BET gas adsorption, X-ray powder diffraction, microcalorimetry and differential scanning calorimetry (DSC). We have found that BET gas adsorption and microcalorimetry being the best methods for distinguishing the different forms of the tested compounds.

Test results

The surface area measured by determining the quantity of a gas (nitrogen) that adsorbs as a single layer of molecules, a monomolecular layer on a sample is formed (Flowsorb II 2300, Micromeritics Co, USA). Surface area after the sample has been standing in high humidity for 24 hrs.

Micronized substance	Non-Conditioned substance	
Conditioned substance		
(m^2/g)	(m^2/g)	(m^2/g)
Terbutaline sulfate:		
11 - 12.5	< 3	7 - 9
Salbutamol sulfate:		
8.4	3	5.9

With the low surface area, obtained when micronized substance has been stored at high humidity, the bulk substance has a great tendency to aggregate when stored, which make the substance very difficult for technical handling in manufacturing the different formulations needed.

The interactions between certain substances and water vapour have also been studied by microcalorimetry. When said substances are subjected to water in the vapour phase they give off heat in a highly cooperative process. This moisture induced phase transition is however not observed for the conditioned substance. Thus, the conditioning process transforms the substance into a more stable form that is less sensitive to humidity.

Comparison of the heat given off by non-conditioned and conditioned substances when subjected to water vapour. Experiments are performed by a Thermal Activity Monitor 2277 (Thermometrics, Sweden).

	Heat (J/g)	
Relative humidity (%)	Non-conditioned substance	
Conditioned substance		
Terbutaline sulfate		
58	3.6	0.1
75	6.2	0.1
Salbutamol sulfate		
75	6 - 8	0.1

When spray-dried lactose has been conditioned in ethanol vapour for 100 hours at room temperature the energy given off was < 0.1 J/g, while the unconditioned lactose loses 40-44 J/g when subjected to water vapour.

The stability of the particles being conditioned were astonishing and will in a remarkable way increase the flexibility of the use of the substance for different formulations.

Experimental procedure

The invention is further illustrated but not limited by the following example.

Example 1

3.6 kg terbutaline sulphate micronized was dried in a stainless steel column with 200 mm diameter at 90°C in vacuum for 23 hours. The dried substance was cooled to about 30°C and the pressure was normalized with ethanol-saturated nitrogen gas. 70 ml/min of ethanol-saturated nitrogen gas was then passed through the 200

mm diameter column for 60 hours to condition the substance. During this time the column was inverted a few times. The residual solvent was eliminated by purging with nitrogen gas for 2 hours and the product, about 3.5 kg, was packed in double plastic bags with a drying agent between the bags.

Example 2

In one experiment 1 g micronized salbutamol sulfate was kept at room temperature for 24 hours in a closed vessel containing a beaker filled with ethanol. The sample was removed and stored in a completely dry environment over night in order to eliminate traces of ethanol. The sample was subjected for analysis (see test results given above).

It is necessary to introduce stirring or tumbling of the substance when conditioning in larger scale.

Example 3

1 g spray-dried amorphous lactose was treated as in exemple 2. The time kept in the saturated ethanol vapour was 100 hours. After removal of residual ethanol, the sample was subjected for calorimetric analysis (see test results given above).

Claims

1. A process for providing water-soluble micronized substances, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such substances, **characterized** in
   a) reducing, if necessary, the residual water from the micronized substance by drying optionally at an elevated temperature and/or vacuum,
   b) conditioning said dried, micronized substances with a solvent, and
   c) eliminating residual solvent by storing in a dry place like vacuum or by purging with an inert gas.

2. A process according to claim 1, **characterized** in that the solvent used in the conditioning step b) is ethanol, acetone or the like, preferably in the vapour phase.

3. A process according to claim 2, **characterized** in that the solvent used in step b) is ethanol.

4. A process according to any one of claims 1-3, **characterized** in that the conditioning step b) is carried out in an inert gas containing solvent vapour.

5. A process according to any one of claims 1-4, **characterized** in that the inert gas used in step c) and optionally in step b) is nitrogen.

6. A process according to any one of claims 1-5, **characterized** in that the substances are additives, such as carbohydrates and amino acids.

7. A process according to claim 6, **characterized** in that the carbohydrates used are lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, xylitol, mannitol, myoinositol or the like and the amino acids used are alanine, betaine or the like.

8. A process according to any one of claims 1-6, **characterized** in that the substances are drugs.

9. A process according to claim 8, **characterized** in that said drugs are antiasthmatic or antiallergic substances.

10. A process according to claim 8, **characterized** in that said antiasthmatic or antiallergic substances are selected from terbutaline sulfate, salbutamol sulfate, fenoterol hydrobromide, bambuterol hydrochloride, terfenadine and disodium chromoglycate.

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 92850062.8

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A1-0 436 110 (BIOCHEMIE GESELLSCHAFT M.B.H.) * page 3, line 17 - line 54 * ---	1-10	A 61 K 9/72
A	US-A-4 405 598 (BROWN K. ET AL) * column 4, line 4 - line 27 * ---	1-10	
A	WO-A1-8 607 547 (GERGELY G. ET AL) * see the whole document * -----	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
STOCKHOLM	16 July 1992	JÖNSSON ANNELI

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO form 1503 03.82

INTERNATIONAL SEARCH REPORT

tional Application No
/GB 03/05353

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 508 969 A (AKTIEBOLAGET ASTRA) 14 October 1992 (1992-10-14) claims 1-10 page 3, line 6 - line 39 examples 1-3	1-18, 21-33

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2004	01/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

INTERN... IONAL SEARCH REPORT

...rmation on patent family members

tional Application No
/GB 03/05353

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0508969 A	14-10-1992	AT	137671 T	15-05-1996
		AT	208613 T	15-11-2001
		AU	662519 B2	07-09-1995
		AU	1534792 A	17-11-1992
		BG	61474 B1	30-09-1997
		BG	98147 A	15-11-1994
		CA	2106975 A1	12-10-1992
		CZ	9302116 A3	13-04-1994
		DE	69210601 D1	13-06-1996
		DE	69210601 T2	02-10-1996
		DE	69232207 D1	20-12-2001
		DE	69232207 T2	01-08-2002
		DK	580648 T3	16-09-1996
		DK	680752 T3	25-02-2002
		EE	2970 B1	15-04-1997
		EP	0508969 A1	14-10-1992
		EP	0580648 A1	02-02-1994
		EP	0680752 A2	08-11-1995
		ES	2086733 T3	01-07-1996
		ES	2168322 T3	16-06-2002
		FI	934429 A	08-10-1993
		GR	3020602 T3	31-10-1996
		HK	52497 A	02-05-1997
		HU	65095 A2	28-04-1994
		IE	921144 A1	21-10-1992
		JP	3400999 B2	28-04-2003
		JP	6506454 T	21-07-1994
		JP	2003155228 A	27-05-2003
		KR	216384 B1	16-08-1999
		NO	933575 A	06-10-1993
		PL	168232 B1	31-01-1996
		PT	680752 T	31-05-2002
		RO	115779 B1	30-06-2000
		RU	2112507 C1	10-06-1998
		WO	9218110 A1	29-10-1992
		SG	43180 A1	17-10-1997
		SK	108893 A3	09-03-1994
		US	5562923 A	08-10-1996
		US	5874063 A	23-02-1999